

Histidine transport dynamics across the healthy human blood-brain barrier investigated by 1H MRS

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Introduction: This study investigates the transport dynamics of Histidine (His) across the blood-brain barrier (BBB) using MRS. In-vivo brain His has been shown to be detectable by MRS after an oral load [1]. His is a large neutral amino acid, occurring naturally in the human body as well as in many foods. It is essential for normal growth, for protein synthesis in general, and is the precursor for the neurotransmitter histamine. This study is of interest as an example to generally characterize the properties of the system L BBB carrier in humans in vivo, which has been studied by MRS for BBB transport of phenylalanine in phenylketonuria [2]. Individual variations of the carrier are under dispute in phenylketonuria [3].

Methods: Four healthy volunteers (27 ± 9 years of age) consumed a single dose of 400mg/kg_{bw} L-histidine in the morning and were followed up with regular blood samplings and MRS measurements for 10 hours. Zinc supplement [4] were provided. An MRS voxel of 45x65x20 mm³ was placed immediately above the lateral ventricle. This location was chosen for the relatively large and uniform volume of the brain (no contribution from ventricles or skull). The large voxel is necessary because of the low intrinsic concentration of histidine in normal human brain. All measurements were performed on a Siemens Trio 3T system using a transmit/receive coil and an optimized PRESS sequence (TE 20 ms, TR 3s, 128 acquisitions/spectrum). Reproducible voxel repositioning was achieved with the product autoalign feature. Spectra were eddy corrected and scaled using non-water suppressed reference scans of multiple TE. Spectra were subjected to HLSVD [5] to remove water and upfield resonances before being modeled in a 2D fashion as a time series [6] with the basic assumption that only histidine content changes between scans. Blood histidine concentrations were measured ex-vivo with mass spectroscopy.

Results and Discussion: Aromatic resonances of brain His become visible after load as seen in Fig 1. Fig 2 shows the time course of blood and brain His concentrations after intake. The blood histidine levels reach a maximum of >3mM, which is ~30 times the normal levels. It appears that each volunteer has different absorption and disposal rates, as indicated by the blood values (2a), but that the influx dynamics into brain is more homogeneous (2b), while the persistence of high brain values is linked to the persistence of high blood values. This suggests that the carrier is strongly saturated and influx is effectively limited by the maximum transport capacity at these blood levels. To visualize the average time course, the data was expressed as % of individual maxima and averaged over subjects (2c). The brain His concentration peaks ~4 hours after its blood content reaches its maximum. There is no immediate evidence of histamine formation from MR spectra (imidazole protons expected to be shifted by 0.05 ppm

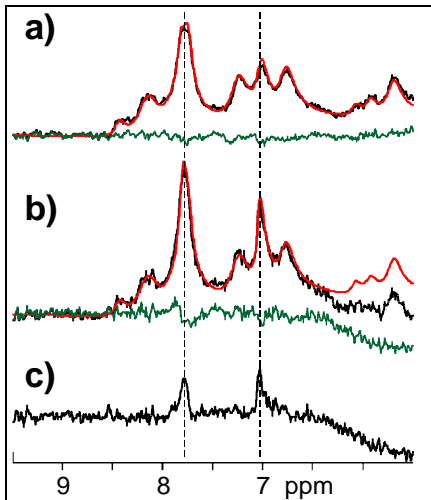


Fig. 1. Original, fitted and residue spectra before (a) and 6 h after load (b) demonstrating data and fit quality in a single subject. Their difference spectrum in c) clearly shows the His aromatic resonance.

vs. His [7]).

Conclusions: Blood and brain histidine levels were measured and it appears that they are linked in each subject, but that the inflow into brain is limited by the maximum BBB transport capacity of the carrier. The brain histidine levels peak ~4 hours after the blood levels.

References: [1] P.Vermathen et al. *Magn Reson Med* 43:665 (2000). [2] H.E.Möller et al. *JCBFM* 18:1184 (1998). [3] J.Pietz et al. *Ann Neurol* 52:382 (2002). [4] A. Takeda, et al. *Biometals*, 15(4):371–5, 2002. [5] T. Laudadio et al. *J Magn Reson* 157:292 (2002). [6] D.G.Q.Chong et al. *25th ESMRMB* #936 (2008). [7] V.Govindaraju et al. *NMRB* 13:129 (2000).

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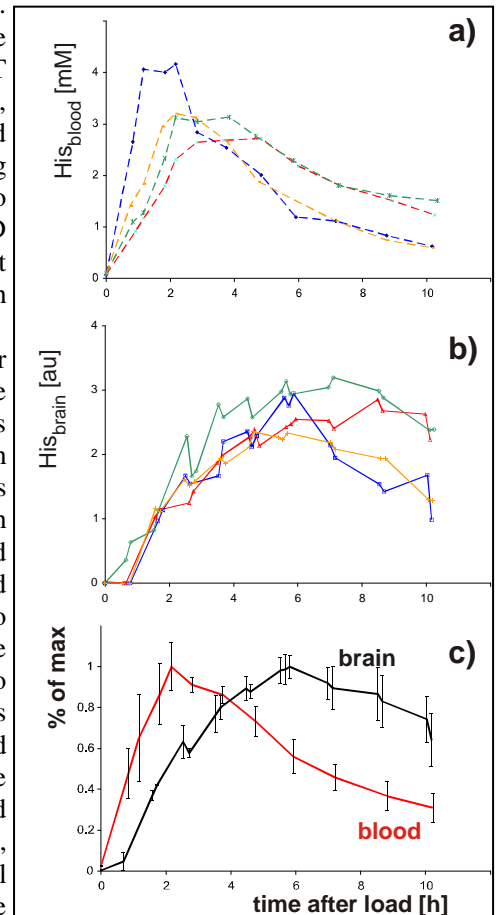


Fig. 2. Individual time courses of blood (a) and brain (b) His levels after the oral load (line color identifies corresponding subjects). (c) contains averaged data (mean \pm sd, scaled as % of individual maximum values).